REMARKS

Applicants submitted a Preliminary Amendment on December 13, 2002 for the instant application. There has been no notice or indication from the USPTO that this amendment has been entered or denied. Applicants therefore are re-presenting the amendments and claims added via the December 13, 2002 Preliminary Amendment.

Claims 1-14 are pending. Claims 1-4 have been amended and previously added claims 13 and 14 are represented from the previously mentioned Preliminary Amendment.

No new matter has been added. Specifically, support for the amendment to claim 3 is provided in the specification at page 8, lines 6-10 and support for previously added claims 13 and 14 is provided in the specification at page 10, lines 12 to 14.

A. Restriction Requirement/ Species Election

Applicants elect Group I without prejudice to pursuing the originally presented or cancelled subject matter in a later application claiming benefit of this application, and particularly without prejudice to determination of equivalents of subject matter of this application or any later application claiming benefit of this application.

The Examiner has also required a species election when Group I had been elected by the Applicants. In compliance with this requirement, Applicants select a species defined by Formula I, wherein B is α-amino-butyric acid, U is (D)-alanine, X is absent, and Y is $COOCH_3$. Claims 1-4, and 9 read on the elected species.

B. Specification/Claim Objections

Applicants have amended the abstract to be clear and concise and in a narrative form not exceeding 150 words.

Applicants have amended the specification to include the terms "chronic obstructive pulmonary disease", "nonsteroidal anti-inflammatory drugs", "dimethylsulfoxide", and "[4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid]," which are well known in the art as definitions

corresponding to the acronyms "COPD", "NSAIDS", "DMSO", and "HEPES" respectively for their first instance of use. Applicants point out that the acronym "HBSS", as used in the specification, stands for "Hank's balanced salt solution", and is spelled out in its first instance of use at page 30, line 26 in the specification.

C. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-4 and 9 are rejected as being indefinite.

The Examiner has alleged that Claim 1 is indefinite due to the recitation of "or a pro-drug." The Examiner has further alleged that the current wording of Claim 1 infers that the applicants are claiming "a cyclosporin analog of formula I or a cyclosporin analog of a pro-drug, or a cyclosporin analog of a pharmaceutically acceptable salt." Applicants respectfully submit that one of ordinary skill in the art would understand claim 1 to mean any cyclosporin analog of formula 1 in claim 1 or its corresponding pro-drug or pharmaceutically acceptable salt of a cyclosporin analog of formula 1 of claim 1. Definitions of "pro-drug" and "pharmaceutically acceptable salt" provide guidance for the selection and preparation of pro-drugs and pharmaceutically acceptable salts of the compounds of the present application. *See* Specification page 16, line 18 to page 17, line 17. Applicants have amended claim 1 to recite, in pertinent part, "A cyclosporin analog of formula 1, or its pro-drug or pharmaceutically acceptable salt." Applicants submit that this amendment clarifies the language of claim 1. Applicants have made similar amendments to claims 2-4 and therefore respectfully request that the Examiner withdraw the present rejection from Claims 1-4.

Claims 1 and 3 are rejected on the additional grounds that the word "or" does not appear before the last recited member of items (i), (ii), (iv), or (v) in Claim 1 nor does it appear before the last recited members of items *i* and *ii* in Claim 3. Applicants have entered the appropriate amendments and submit that the rejection no longer applies to Claim 1, 3, or dependent claims thereof, as amended.

Claim 3 has also been rejected as being indefinite as missing "," between "halogen substituted C1-C6" and "alkylthio" (Action page 6, lines 16-17). Applicants respectfully

request that this rejection be withdrawn because the last member recited is "halogen substituted C1-C6 alkylthio" rather than "alkylthio."

The Examiner has alleged that Claim 9, in reciting "at least one cyclosporin" renders the claim indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as their invention. Applicants disagree. The M.P.E.P. § 2173.05 (h) (II.) states acceptable alternative expressions not in violation of 35 U.S.C. § 112, second paragraph. *See* MPEP §2173.05 (h) (II.)(citing In re Gaubert, 524 F.2d 1222 (CCPA 1975)). Among the acceptable phrases under Gaubert is the phrase "at least one piece." *See* M.P.E.P. § 2173.05 (h) (II.) (citing Gaubert, 524 F.2d at 1227). Applicants submit that this phrase is exactly analogous to the phrase "at least one cyclosporin analog" used in Claim 9 of the instant application. Thus, it is established that the phrase "at least one _____" meets the requirements of 35 U.S.C. § 112 , second paragraph. Applicants therefore respectfully request that the rejection be withdrawn from Claim 9.

D. Rejections Under 35 U.S.C. § 102(b)

Claims 1-4 and 9 are rejected as being anticipated by Wang, N.Y. *et al.*, US Patent No.: 5,427,960 ("Wang"). It is stated in the action that:

> Wang *et al.* disclose a cyclosporin structure that meets the limitations of the Formula (I) structure of claim 1 of the instant application (see column 6, formula I, wherein "R^1", "R^2", and "R^3" = H (see line 570); "R^4" = $C(R^5R^6)$-W_r-$(C=Y)_m$-Z, wherein R^5 and R^6 are "H" (see line 60), "r" = 0 (see lines 52-59), "Z" is OR_a (*a* = 1 carbon atom, *i.e.*, CH_3, see lines 67-68), "Y" is "O" (see lines 47-48); thus, R^4 would be $-CH_2$-CO-[O]CH_3. Since Applicant elects "B" as -α-amino butyric acid, "U" as –(D) alanine, "X" is absent, and "Y" as $COOCH_3$ for patent examination, claims 2-4 are anticipated by the patent reference as well. (Action, page 7)

Applicants disagree. For a generic chemical formula of compounds to anticipate a claimed species covered by the formula, the species must be "at once envisaged" from the formula. *See* MPEP § 2131.02 (citing In re Petering, 301 F.2d 676, 133 U.S.P.Q. 275 (CCPA 1962). Stated differently, "anticipation can only be found if the classes of substituents are

sufficiently limited or well delineated (emphasis added)." *See* MPEP § 2131.02 (citing *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990)).

Applicants submit that the elected species of the instant application cannot be "at once envisaged" from formula I of the Wang reference, and therefore is not anticipated by Wang. To define the Applicant's elected species, the Examiner was forced to define 12 separate variables described in formula I of the Wang reference. The large number of variables that must be explored to arrive at the elected species of the instant application provides evidence that one of ordinary skill in the art would not be able to "at once envisage" said elected species. Formula I of the Wang reference sets forth three alternate definitions of R^1, R^2, R^3, and R^4 under subsections (1) – (3), in which variables R^1, R^2, R^4, W, and Z each encompass a very large number of possible substituents. In addition, subsections (1)-(3) of formula I initially define Z as a "poly(amino acid)" or a "polyamino acid derivative" or a "fluorescent moiety." Not until the last sentence defining formula I is Z redefined to encompass the possibility of forming the elected species. Due to the extensive exploring of formula I, and the variables broadly defined therein, to define the elected species, Applicants submit that the elected species cannot be "at once envisaged," from formula I of Wang. Thus, in accordance with M.P.E.P. § 2131.02, the Wang reference cannot anticipate the Applicant's elected species. Applicants therefore respectfully request that the Examiner withdraw the rejection of Claims 1-4, and 9.

Claim 8 is also rejected as being anticipated by Wang. It is alleged in the Action that:

> Wang et al. teach a carrier that is a poly(amino acid) or bovine serum albumin (see column 3, lines 42-50), as applied to claim 8 of the current application (Office Action, page 4).

Applicants disagree. The uses of the term "carrier" in Wang and in Applicants' claim 8 are distinguishable and different. The pharmaceutical composition of claim 8 comprises "a cyclosporin compound of claim 1 together with a pharmaceutically acceptable diluent or carrier therefor." The specification clearly defines the term "pharmaceutically acceptable

carrier" to mean "a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type" (Specification, page 17, line 23 through page 18, line 1). Thus, the composition contains a cyclosporin compound and a distinct and separate, e.g., filler, substance.

Wang *et al.* teach a carrier that is a poly(amino acid) or bovine serum albumin. However, the term "carrier" as used in Wang refers to a carrier molecule that is covalently linked to a cyclosporin-based hapten:

> The present invention also relates to novel cyclosporin A compounds substituted at and conjugated to an antigenicity-conferring carrier through a derivative formed at the first amino acid residue...The preferred carrier is a poly(amino acid), most preferably bovine serum albumin (BSA) (Wang at column 3, lines 42-45; lines 48-50).

> Thus in the case of cyclosporin A derivatives bearing a reactive functional group this will be any group capable of reaction with a carrier molecule, e.g., a protein molecule, to provide a co-valently linked conjugate with said carrier molecule...(Wang at column 6, lines 12-17).

> The immunogens of the present invention are made by coupling a hapten, such as that shown in Formula (II), to a poly(amino acid)....In the preferred embodiment, the poly(amino acid) is bovine serum albumin (BSA)...(Wang at column 9, lines 24-27 and lines 31-33).

Clearly the meaning of the term "carrier" in Wang is distinct and different from the meaning of the term in Applicants' claim 8. In Wang, "carrier" refers to an antigenicity-conferring molecule that is covalently linked to a cyclosporin. On the other hand, the term "carrier" as used in Applicants' claim 8 refers to a non-covalently linked, inert substance that serves the role of a non-toxic filler, diluent, etc. for a cyclosporin-containing pharmaceutical composition. Applicants' cyclosporin structure is not covalently linked to the "carrier" in their composition, while Wang's compounds are, in fact, carrier-linked cyclosporin derivatives (i.e., polyaminoacid or BSA conjugates). Thus, Applicants submit that Wang does not anticipate claim 8. Applicants therefore respectfully request that the rejection be withdrawn.

E. Provisional Rejections-Obviousness Type Double Patenting

Claims 1-4 and 9 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-4 and 11 of copending Application No. 09/976219 and claims 1-4 and 11 of Application No. 09/9800856. (Action page 7).

Applicants disagree with the assertions in the Action regarding obvious structural variation. Applicants will address these issues upon maturation of any of the instant or cited applications into a granted patent.